duction. 5) Platelets can be regarded as the target cells for HC, since it was proved that they participate in the inflammation response.

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Abnormal Sleep Pattern and Impaired Learning Capacity in Rats with MPTP-Induced Parkinsonian Syndrome

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Rats with the Parkinsonian syndrome induced by systemic injection of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) develop extrapyramidal disorders (oligokinesia, tremor, and rigidity) which depend on the dose and duration of action of MPTP. At 15 and 30 mg/kg MPTP impairs the learning of the conditioned passive avoidance response, shortens both stages of sleep, particularly the paradoxical (REM) stage, and prolongs the period of wakefulness. The mnestic function disturbance is not associated with extrapyramidal disorders, since it develops in their absence. In MPTP-treated rats memory and sleep disorders are interrelated.

Key Words: *extrapyramidal disorders; Parkinsonian syndrome; sleep pattern*

In addition to extrapyramidal symptoms (tremor, oligokinesia, and rigidity) and characteristic autonomic disturbances, patients with parkinsonism have impaired intellectual and mnestic functions and develop sleep disorders [5-8]. The causes of these abnormalities and their relation to pathogenesis and therapy of Parkinson's disease so far remain unclear. The Parkinsonian syndrome has been modeled with the use of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin which damages dopaminergic neurons of the striatum thus inducing extrapyramidal disturbances [2,9]. Chronic administration of MPTP in low doses to monkeys impairs the learning of conditioned responses, the effect being reversed by dopaminergic agonists [10].

In this study we examined mnestic functions and sleep disorders in rats with the Parkinsonian syndrome induced by MPTP.

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MATERIALS AND METHODS

The study was conducted on random-bred male rats (body weight 220-250 g) maintained on standard diet under standard vivarium conditions. The Parkinsonian syndrome was induced by intraperitoneal injection of 15 or 30 mg/kg MPTP [1]. At different times postinjection, extrapyramidal disturbances were recorded. The motor activity was measured for 10 min in an actometer. Tremor and rigidity were scored in points. The presence or absence of clonic-tonic convulsions, salivation, piloerection, and diarrhea were noted. Neurologic deficiency and muscle tone were evaluated in tests of climbing on a net, holding onto an overturned platform, pulling up on a horizontal bar, and running along a ruler supported in a horizontal position by two cross bars at a height of 70-80 cm. As the learning test, we used a procedure in which rats developed a conditioned passive avoidance response (CPAR) in a chamber divided into two compartments, one of which was illuminated and the other was not [10]. Stages of sleep were analyzed from a 5-h EEG [1].

RESULTS

The effects of MPTP on the locomotor activity and neurological status of rats were found to depend on the age of the animals, MPTP dose, and duration of MPTP action. In a dose of 5 mg/kg MPTP had no effect on the hole reflex judging from the net climbing test and neurological status. At 15 mg/kg MPTP slightly impaired the rats' ability to pull up on the horizontal bar and hold onto the overturned platform but had no effect on the hole reflex and the ability to run along the ruler. By the 90th min postinjection, the performance of MPTP-treated rats in all tests was slightly worse compared with the controls, and oligokinesia (manifested as a 3-fold decrease in motor activity) had developed. Oligokinesia markedly decreased 24 h after injection (Table 1).

At 30 mg/kg MPTP induced pronounced psychomotor disturbances whose severity depended on the duration of the neurotoxin action. Convulsions of the trunk, tremor, salivation, and the Schtraube's syndrome were observed after 10-15 min. After 90 min, the Schtraube's syndrome and convulsions disappeared, and tremor and salivation decreased considerably. During this period, rigidity and severe oligokinesia developed (Table 1). After 24 h, tremor disappeared, rigidity and oligokinesia became much less pronounced, and the rats were capable of learning the CPAR.

Administration of 15 mg/kg MPTP 15 min before the rats started learning the CPAR complicated the learning process, as evidenced by an increase in the number of runs necessary to acquire this response. However, the latency of the first entry of MPTP-treated rats into the dark compartment did not differ from that of intact controls, indicating that their motor functions were preserved during this period (Table 2). Ninety minutes after administration of 15 mg/kg MPTP, oligokinesia in some animals hindered the development of the conditioned response. Two out of 8 rats failed to enter the dark compartment over a 3-min observation period. As shown in Table 2, the latency of the first entry into the dark compartment in these rats was much longer than in the controls, indicating inhibition of motor functions. On the other hand, the rats capable of acquiring the conditioned response learned it after the first entry into the dark compartment (Table 2).

Injection of 30 mg/kg MPTP resulted in disappearance of tremor and considerably reduced rigidity and oligokinesia 24 h postinjection. These rats entered the dark compartment after a longer latent

TABLE 1. Extrapyramidal Disturbances Induced in Rats by MPTP (*M±m*)

Extrapyramidal disturbance	Time of analysis	MPTP dose	
		15 mg/kg	30 mg/kg
Oligokinesia (motor activity for 2 min)	Before MPTP injection (control)	34.5±3.2	32.7±2.4
	90 min after MPTP injection	11.7±2.8**	9.8±2.8**
	24 h after MPTP injection	25.8±4.5	18.6±1.8*
Rigidity	Before MPTP injection (control)	-	-
	90 min after MPTP injection	±	++
	24 h after MPTP injection	-	±
Tremor	Before MPTP injection (control)	-	-
	90 min after MPTP injection	-	±
	24 h after MPTP injection	-	-

Note. *$p<0.05$, **$p<0.01$ compared with the control.

TABLE 2. Effect of MPTP on the Ability of Rats to Develop the Conditioned Passive Avoidance Response (*M±m*)

Group	Number of entries during learning	Latency, sec	
		during learning	during testing
Control rats	1	29.9±6.93	145.3±14.7**
Rats given MPTP before learning:			
15 mg/kg 15 min before	1.75±0.7	26.8±8.82	100.5±12.6**+
15 mg/kg 90 min before	1	49.3±2.73+	104.2±11.55**
30 mg/kg 24 h before	1.43±0.07	68.11±9.38+	103.4±8.61+

Note. *$p<0.05$, **$p<0.01$ relative to the latency during learning; +$p<0.05$ relative to the latency in the control.

TABLE 3. Effect of MPTP on the Sleep-Wake Cycle (%) in Rats (*M±m*)

Group	NREM	REM sleep	Wakefulness
Control rats	53.97±9.5	13.05±4.3	31.9±5.3
Rats given MPTP at 30 mg/kg:			
after 1.5 h	21.2±3.8**	1.9±0.4***	76.9±9.7**
after 24 h	51.6±5.6	4.2±0.9**	44.2±5.7*

Note. *$p<0.05$, **$p<0.001$, ***$p<0.001$ in compared with the control.

period than did the controls and make more runs to elaborate the CPAR (Table 2).

Analysis of how the rats performed the CPAR 24 h after acquiring it showed a markedly impaired response. MPTP-treated rats showed much longer latency of entry into the dark compartment compared with the controls. Thus, these rats were less capable of learning the conditioned response in comparison with intact rats. MPTP deteriorated the response reproduction to a greater extent than its learning.

In the sleep-wake cycles, both stages of sleep became much shorter 1.5 h after 30 mg/kg MPTP. The REM stage was more inhibited than the NREM stage and disappeared completely in some animals (Table 3). Spectral analysis of electrical activity on corticograms and hippocampograms during that period revealed severe disturbances of the hippocampal θ rhythm, as evidenced by enhanced slow-wave component of this rhythm (4-7 Hz) and reduced fast-wave component (8-12 Hz). Twenty-four hour after MPTP administration, the NREM stage tended to increase, while the proportion of wakefulness in the sleep-wake cycle decreased, but both still differed from their control levels; the proportion of REM episodes remained low (Table 3).

This study showed dissociation in time of extrapyramidal and mnestic disturbances and sleep disorders in rats injected the neurotoxin MPTP. Changes in learning and memory developed earlier than did extrapyramidal disturbances. A temporal correlation was found between the development of sleep and memory disorders. When extrapyramidal abnormalities were at their peak (90 min after MPTP injection), the learning process was changed to a lesser extent. Cognitive functions are probably more sensitive to MPTP than motor functions: alterations of cognitive functions were developed earlier and lasted longer. Our results agree with the observation [9] that MPTP injection results in deterioration of the conditioned reflex activity in monkeys in the absence of pronounced motor disturbances. Neurochemical studies show that the serotonin content in the raphe nuclei increases 15 min after MPTP injection and remains elevated for 2 h [3]. The MPTP-induced changes in the function of the serotoninergic system and degeneration of dopaminergic neurons are probably a key mechanism responsible for the impairment of learning and sleep structure in animals with experimental Parkinsonian syndrome.

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